

# **REMARKS**

With the entry of the present Amendments, Claims 1-3 are pending in the Application. Claims 4 and 5 have been cancelled. In view of the remarks that follow, Applicants respectfully request that all of the pending rejections be withdrawn.

## ***I. Rejection of Claims Under 35 U.S.C. § 103(a) Over Ruth in View of Roberts***

In the Office Action, Claims 1, 4 and 5 were rejected under 35 U.S.C. § 103(a) as unpatentable over Ruth, et al. (J. of Rad. and Nuclear Chem., **1996**, *203*, 457-469, hereinafter “Ruth”) in view of Roberts, et al. (Res. and Indus., **1999**, 1006-1009 no. 475, hereinafter “Roberts I”). In support of this rejection, the Examiner states that Ruth teaches the <sup>18</sup>F-fluorination of alkanes, but does not teach an <sup>17</sup>F-labeled alkane having two or more carbon atoms. The Examiner also states that Roberts I teaches “an <sup>17</sup>F-labeled fluoromethane generated from <sup>17</sup>F and CH<sub>3</sub>Br that shows great promise as an improved tracer for regional cerebral blood flow measurements with PET.” (Office Action, page 2) Based on these observations, the Examiner concludes that it would have been obvious for one ordinarily skilled in the art to use <sup>17</sup>F as a radio label in the PET imaging agents disclosed by Ruth to gain the advantage taught by Roberts I. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, three criteria must be met: 1) the cited references must provide some motivation or suggestion to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the resulting combination must teach or suggest all of the limitations of the rejected claims. (M.P.E.P. § 2142) The combination of Ruth and Roberts I fails to provide a *prima facie* case of obviousness because the substitution of <sup>17</sup>F for the <sup>18</sup>F in the methods disclosed by Ruth could not be based on a reasonable expectation of success.

As a preliminary matter, Applicants respectfully submit that the Examiner has inadvertently cited the incorrect reference in support of this rejection. Roberts I does not teach an <sup>17</sup>F-labeled fluoromethane generated from <sup>17</sup>F and CH<sub>3</sub>Br that shows great promise as an

improved tracer for regional cerebral blood flow measurements with PET. However, this teaching does appear in the poster presentation, A. D. Roberts, K. A. Dabbs, A. K. Converse, R. J. Nickles, and M. J. Schueller, "Production of the Short-Lived Flow Tracer Fluorine-17 Fluoromethane From Proton Irradiation of Neon," presented at the 47th Annual Meeting of the Society of Nuclear Medicine in St. Louis, Missouri on June 3-7, 2000 (hereinafter "Roberts II"). With regard to Roberts II, Applicants respectfully direct the Examiner's attention to the accompanying Declarations of Alexander K. Converse, Kevin A. Dabbs, and Michael J. Schueller, which are submitted under 37 C.F.R. § 1.132. Applicants hereby request that these Declarations be entered into the file of this Application and be made of record. These Declarations were originally filed in the parent patent application (serial number 09/845,639; now issued Patent no. 6,585,953) in an Amendment and Request for Consideration mailed on January 17, 2003. At the time the Amendment and Request for Consideration was filed, pending Claims 1-3 were pending in the parent patent application as Claims 43-45.

Alexander K. Converse, Kevin A. Dabbs, and Michael J. Schueller are the co-authors, along with the two inventors, of Roberts II. This poster presentation, which includes Alexander K. Converse, Kevin A. Dabbs, and Michael J. Schueller as authors in addition to the inventors of the present application, occurred prior to, but not more than one year before, the filing date of the parent patent application from which the present patent application claims priority (as a divisional). However, the enclosed Declarations of Alexander K. Converse, Kevin A. Dabbs, and Michael J. Schueller confirm that these three authors are not inventors, either solely or jointly, of the subject matter claimed in the present application. For this reason, Roberts II is not prior art that can be asserted against the claims of this application. With the removal of Roberts II as prior art, the pending rejection has been overcome and Applicants respectfully request that this rejection be withdrawn.

The Examiner has not identified any language from Roberts I that would provide a suggestion or motivation to replace the  $^{18}\text{F}$  in the methods of Ruth with  $^{17}\text{F}$ . Moreover, even if such language could arguable be identified, it would be insufficient to provide motivation to

make such a substitution because the very short half-life of  $^{17}\text{F}$  makes it impossible to incorporate  $^{17}\text{F}$  into the organic molecules of Ruth using the methods disclosed therein to an extent that would render the resulting molecules suitable for use in medical imaging. Therefore, one of ordinary skill in the art could not reasonably expect the substitution suggested by the Examiner to succeed.

The half life of  $^{17}\text{F}$  is a very short 64 seconds. By comparison, the 110 minute half life of  $^{18}\text{F}$  is quite long. As one of ordinary skill in the art would understand, many radiolabeling reactions used to label organic molecules with  $^{18}\text{F}$  simply will not work for  $^{17}\text{F}$  because the half life of  $^{17}\text{F}$  is much too short. This the case for the reactions described in Ruth. On pages 462-465, Ruth describes electrophilic and nucleophilic reactions used to produce  $^{18}\text{F}$ -labeled organic molecules. It is impossible to use the electrophilic and nucleophilic reactions of Ruth to incorporate  $^{17}\text{F}$  into organic molecules because so much of the  $^{17}\text{F}$  would be lost during production that the resulting molecule would be unsuited for use as a radiopharmaceutical. This conclusion is supported by the accompanying Declaration of Robert J. Nickles (hereinafter "the Nickles Declaration"). The Nickles Declaration explains that the  $^{18}\text{F}$  in the electrophilic and nucleophilic reactions of Ruth could not be replaced by  $^{17}\text{F}$ .

Unlike the conventional reactions described by Ruth, the present application describes continuous, on-stream methods for producing  $^{17}\text{F}$  labeled fluoroalkanes that are fast enough to produce  $^{17}\text{F}$  labeled alkanes for use as radiopharmaceuticals. For example, paragraphs 0040 and 0041 describe methods of preparing  $^{17}\text{F}$  labeled fluoroalkanes by contacting  $^{17}\text{F}$  labeled  $\text{F}_2$  with alkanes, alkenes or alkynes in the presence of a metal oxide catalyst.

Therefore, because one of ordinary skill in the art would not reasonably expect to successfully replace the  $^{18}\text{F}$  of Ruth with  $^{17}\text{F}$ , as suggested by the Examiner, Applicants respectfully submit that the combination of Ruth and Roberts I does not render independent Claim 1 unpatentable, and respectfully request that the pending rejection be withdrawn.

## *II. Rejection of Claims Over Pike in View of Roberts and/or Mulholland*

Claims 1-5 were rejected under 35 U.S.C. § 103(a) as unpatentable over Pike, et al. (Drug Metab. Dispos., **1995**, 23, 832-839, hereinafter “Pike”) in view of Roberts I and/or Mulholland, et al. (J. Nuc. Med., **1987**, 8, 1082, Posterboard 899, hereinafter “Mulholland”). In support of this rejection, the Examiner asserts that Pike teaches an  $^{18}\text{F}$ -labeled 1,1,1,2-tetrafluoroethane, but does not teach a  $^{17}\text{F}$ -labeled 1,1,1,2-tetrafluoroethane. The Examiner further asserts that Roberts I teaches a  $^{17}\text{F}$ -labeled fluoromethane generated from  $^{17}\text{F}$  and  $\text{CH}_3\text{Br}$  that shows great promise as an improved tracer for regional cerebral blood flow measurements with PET. (Office Action, page 2) The Examiner still further asserts that Mulholland teaches the synthesis of  $^{17}\text{F}$  fluoromethane. Based on these observations, the Examiner concludes that it would have been obvious to one ordinarily skilled in the art to combine the information taught by Pike, Roberts and/or Mulholland to generate a 1,1,1,2-tetrafluoroethane with at least one of the F atoms being a  $^{17}\text{F}$  with a reasonable expectation of success. Applicants respectfully traverse.

Again, Applicants respectfully submit that the Examiner has identified the wrong Roberts reference in support of this rejection. The language relied upon by the Examiner in support of this rejection actually appears in Roberts II, which has been removed as a prior art reference by the accompanying Declarations submitted under 37 C.F.R. § 1.132. The Examiner has not identified any language in Roberts I that provides a suggestion or motivation to modify the teachings of Pike. For this reason, Applicants respectfully request that the rejections based on Roberts I be withdrawn.

With regard to the remaining rejections, as described in Section I above, the very short half-life of  $^{17}\text{F}$  makes it impossible to substitute  $^{17}\text{F}$  for  $^{18}\text{F}$  in many radiolabeling methods. Like Ruth, Pike teaches nucleophilic reactions for producing  $^{18}\text{F}$ -labeled organic molecules, specifically  $^{18}\text{F}$ -labeled 1,1,1,2-tetrafluoroethanes. However, the very short 64-second half-life of  $^{17}\text{F}$  makes it impossible to successfully replace the  $^{18}\text{F}$  in the reactions of Pike with the  $^{17}\text{F}$  disclosed in Roberts I or Mulholland, because the resulting product would not retain a sufficient amount of  $^{17}\text{F}$  to be useful as a radiopharmaceutical. Again, this conclusion is supported by the

Nickles Declaration which explains that the  $^{18}\text{F}$  in the nucleophilic reactions of Pike could not be replaced by  $^{17}\text{F}$ . Therefore, the combination of Pike, Roberts I and/or Mulholland fail to render rejected independent Claim 1 obvious and Applicants respectfully request that this rejection be withdrawn.

For the foregoing reasons, Applicants respectfully submit that all of the claims pending in the Application are now in condition for allowance. Consequently, Applicants respectfully request that the Examiner withdraw all of the rejections and allow the Application to issue.

The Examiner is invited to contact the undersigned by telephone if it is thought that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-2350. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-2350.

Respectfully submitted,

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